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Editorials

THE CURRENT STATUS OF HYPOTHERMIA

THERE are rumbles in the background suggesting that a storm is brewing—that a new concept of the significance of the human organism's response to trauma is evolving which might lead to new techniques for solving many major problems in the management of the sick patient. From France one hears of "artificial hibernation," of "slow-motion life," of "sympathetic neuroplegia"; in Britain "hypotensive anesthesia" has become common practice; in the United States "general hypothermia" is creeping into the armamentarium of the cardiac surgeon. What is the conceptual relationship among these techniques, if any, and what is the evidence to support them? What biological kinship exists between the pharmacologic "lytic cocktail" and the physical agent ice-water? Herein, at the present time, lies the confusion of a welter of undocumented theories. Yet an underlying hypothesis of great attractiveness appears dimly, seeking to be established or refuted, not by claims and rash clinical trial, but by vigorous and careful research.

The imaginative originator of the "French cocktail" and spokesman for an enlarging group of Parisian anesthesiologists is the biologist Laborit.¹ He has described the hypothesis in broad outline somewhat as follows: Warm-blooded mammals, and particularly man, have evolved into a state of relative freedom from their environment through the development of a complex mechanism of response to noxious stimuli designed to maintain in the body certain constants, geared to promote the capacity for fight or flight. This is the *milieu interne* of Bernard; the "homeostasis" of Cannon. These reactions are mediated through a so-called neuro-endocrine system and have as their objective the maintenance of a state of environmental freedom. It is alleged that these reactions, occurring at high metabolic rates, require energy from intrinsic sources and that in time exhaustion may ensue. The organism in its effort to maintain its freedom loses its life through exhaustion. The same energy, it is postulated, if conserved by acquiescence to environment at a diminished metabolic level, might serve to overcome the noxious stimulus and permit survival.

Here is romance in biology! Yet from this concept, eloquently expounded and adorned by a growing armamentarium of little-understood pharmaceutical agents, has sprung a rash of clinical applications, from which, in turn, great claims have been made. The "lytic cocktail," containing from three to eight different drugs and varied at the whim of the physician, is administered over a period of days to patients with a variety of diseases. Operations may be performed. It is then alleged that these patients would not have survived their disease and its treatment had they not been subjected to polypharmacy. It is true that the drugs have effected a change

in the patient, simulating drugged sleep. He is lethargic and moves but little; his pulse and blood pressure are decreased; pain response is dimmed; emotional reaction is lost. Vital functions, however, persist. He usually survives.

How one wishes to see some objective studies of this fascinating state of narcolepsy! It is stated that metabolism is markedly reduced; yet no studies of oxygen consumption are displayed. It is stated that overwhelming infection is overcome without the usual response to such aggression; yet no studies of the effect of the "cocktail" on the mortality of experimental infections have apparently been made. It is alleged that the "cocktail" alters the metabolic response to trauma; yet no studies of this response (which is being so elaborately documented in many laboratories in this country) have apparently been undertaken. The term "sympathetic neuroplegia" suggests paralysis of the sympathetic and/or parasympathetic systems, but no testing of sympathetic functions documents this statement. The word "hibernation" has been used; yet the published data on body temperatures reveal a drop from the normal 37 C. (98.6 F.) of only 0.5 to 3 degrees (C.). This temperature level is known to have only slight effect upon metabolism and is a far cry from the hibernating animal, whose temperature may be in the neighborhood of 4 to 10 degrees (C.). It is apparent, then, that a state of skepticism regarding this bold theory will remain until some scientific evidence is submitted to lift it from the realm of philosophy. From the point of view of hypothermia, however, it must be emphasized that the French are describing a state in which body temperature is only slightly below normal.

On the other hand, it is remarkable to read of the capacity of the human to survive the simultaneous administration of a multitude of cellular toxins. Moreover, this rather specific evaluation of the significance of the neuroendocrine response to trauma is important. Many workers have elaborately described the multiple manifestations of this response, but few, at present, can quantitate the importance of any of these manifestations in terms of survival or recommend in therapy whether it is better to suppress or abet them. Because Laborit's theory has not been proved to be right does not necessarily mean that it is totally wrong, and in the efforts which must follow to evaluate the concept, important light may emerge on this crucial question.

From Britain has recently appeared an important study of the relation between the "lytic cocktail" and hypothermia. Previous work there had been largely concerned with the use of hypotensive anesthesia as a means of reducing hemorrhage during certain operative procedures. Hypothermia was not involved except by analogy. Pharmacologic hypotension at levels of 70 to 100 mm. Hg systolic pressures were demonstrated to be well tolerated by the anesthetized human. Hypothermia in the range between 35 and 20 C. (95 and 68 F.) causes progressive lowering of systolic blood pressure to levels of 30 to 60 mm. Hg, with tissue and organ survival. Both methods, apparently, result in a form of "physiologic," or survivable, hypotension. Dundee and his co-workers, in Liverpool,² however, studied in both dogs and patients the effect of (1) hypothermia on metabolic rate, (2) each agent of the "lytic cocktail" on the cooling process, and (3) the "lytic cocktail" on cooling and on metabolic rate. As regards the first, they confirmed the previous work of Martin³ and of Bigelow and his associates,⁴ by demonstrating that in the absence of shivering a definite relation exists between body temperature and oxygen consumption, metabolism dropping about 5% for each degree Centigrade

down to 27 C., and less rapidly thereafter. Secondly, of the three components of the "cocktail," Pethidine (meperidine hydrochloride) "vagolytic," Avomine (promethazine chlorotheophyllinate) "sympatholytic," and Chlorpromazine "CNS-depressant," only the last appeared to enhance the speed of cooling, and this apparently only through inhibition of shivering. Deep anesthesia and curarization were essentially as effective in promoting hypothermia. Thus the importance of inhibition of muscle activity to allow cooling (Smith and Fay⁵) was confirmed. Thirdly, the cocktail itself resulted in a fall of body temperature rarely in excess of 2 degrees C. (averaging 0.5 degree C.), and oxygen consumption fell by only 8 or 10%. Thus the claims that the cocktail specifically lowers metabolism remain unconfirmed. The 26 patients studied were cooled moderately (only five below 31.5 C.) and subjected to major operations while hypothermic. Their ages varied from 23 to 77 years. Five deaths occurred in the series.

It is surprising how little of the physiology of cold and of hypothermia is known. To Bigelow, in Toronto, must go the credit for rekindling interest in this modality by the report from his laboratory in 1950 of the survival of dogs cooled to 20 or 25 C., in which circulation was totally arrested for 15 minutes. Since then, several laboratories in this country and abroad have turned attention to the study of this problem. One must keep clearly in mind the distinction between "cold" and "hypothermia." Cold is a physical state. When used as a description of the intimate environment, warm-blooded creatures respond to cold by efforts to maintain their temperature. This involves muscle activity, high cardiac output, and high oxygen consumption. Cold is thus a vigorous stimulus. This response, however, may be depressed by deep narcosis or curarization. Then hypothermia, a term describing the state of a homothermic animal with a subnormal body temperature, may ensue. Hypothermia, obviously, may be of different degree (i. e., any body temperature between the normal and absolute zero). In the area from 37 C. (98.6 F.) down to 20 C. (68 F.), there appears to be agreement on the following essentials.

Body temperature can be lowered by a variety of cold agents, provided shivering is prevented. Under these conditions, metabolic activity falls progressively as the body cools. There are associated changes in circulation, the heart rate slowing, blood pressure falling, and cardiac output diminishing. Respirations also become slower and at some point will cease entirely. From this point on, artificial respirations must be established if life is to be maintained. In temperature ranges below 28 C., anesthesia of sufficient depth to allow operative procedures is accomplished. Major organ function continues, and above 20 C. no specific cellular pathology occurs within periods of several hours. The temperature range free of organic disturbance may even extend much lower, but the area 20 to 5 C. has not been sufficiently studied for one to be sure. Age is apparently an important factor, since the very young tolerate deep cooling more safely than adults. Also, certain species of mammals are capable of surviving prolonged periods of remarkably low body temperature.

Hypothermia, however, has serious inherent risks and if carried far enough at the present will be uniformly lethal. Death apparently results from one of two mechanisms. The first is ventricular fibrillation. It seems that the fibrillatory threshold is lowered by hypothermia itself, although the mechanisms are not clear. In the dog and in man, below 28 C. ventricular fibrillation becomes increasingly common, and as the temperature falls below 20 C. this eventuality may be uni-

formly expected. The other mechanism is primarily the end-point of asphyxia. As the temperature falls, spontaneous respirations may cease, resulting in hypercapnia and hypoxia. Cardiac arrest, often followed later by ventricular fibrillation, will result. The mechanisms underlying this myocardial response to cold are obscure. As regards primary fibrillation, studies in our laboratory have suggested that membrane permeability to potassium may be an important factor. The cholinesterase enzyme system may be involved, since use of an anticholinesterase significantly raises the fibrillatory threshold.*

In any event, general hypothermia is capable of significantly reducing metabolism and of producing a "physiologic" hypotension. As such, the use of this modality suggests itself as potentially valuable in a variety of conditions. Some of these possible uses are tabulated in the following outline.

- I. To reduce oxygen need in reversible conditions causing hypoxia
 - A. Acute pulmonary diseases interfering with respiration (pneumonia, atelectasis, etc.)
 - B. Pulmonary, cerebral, or peripheral embolus
 - C. Anemic crises (acute erythropenia)
 - D. Congenital cyanotic heart disease
 - E. Lower nephron oliguria
 - F. Deliberate temporary interruption of blood supply
 1. Total interruption
 - a. Cardiac surgery
 2. Regional interruption
 - a. Descending aorta
 - 1 Hepatectomy
 - 2 Aneurysm
 - 3 Massive visceral excision
 - b. Carotid artery
- II. To produce "physiologic" hypotension
 - A. To diminish operative hemorrhage
 1. Brain
 2. Middle ear (fenestration)
 3. Massive skin grafting
 - B. To reduce internal hemorrhage
 1. Duodenal ulcer
 2. Esophageal varices
 - C. To counteract hypertensive crises
 1. Encephalopathy
 2. Eclampsia
- III. To reduce oxygen need and produce "physiologic" hypotension:
 - A. Shock
 1. Traumatic
 2. Sepsis
 3. Nonseptic peritonitis
 - B. Myocardial infarction
- IV. To specifically combat hyperpyrexia:
 - A. Thyrotoxicosis
 - B. Third-ventricle hemorrhage
 - C. Heat stroke
 - D. Severe infection

* References 6 and 7.

At the present time, however, this tabulation must be considered as an outline for research, since few if any careful studies exist in most areas. Indeed, it may be hopelessly optimistic. In Group I, *D* and in Group I, *F*, a volume of encouraging experimental and clinical experience is accumulating in various hospitals throughout the country. McQuiston⁸ first reported the protective effect of very mild hypothermia (1 to 3 C.) in the operative management of cyanotic heart disease. Muller (in the discussion on the article of Swan and co-workers⁶) and Dagliotti⁹ have advocated more pronounced cooling for the same purpose. Cookson and his associates¹⁰ and Lewis and Taufic¹¹ have attempted open-heart procedures during cessation of circulation under hypothermia. I have recently completed the study of a series of 45 patients with a variety of open-heart procedures, with nine deaths. The other applications of the technique, however, remain to be studied.

Hypothermia is still highly experimental. It may hold great promise, yet it must be considered as a procedure involving inherent risks. Much basic research must be done to elucidate the dangerous myocardial reaction. Careful observations of the body response to hypothermia (not cold) and to its variations from the expected norms under various conditions are needed. Throughout these studies, variables must be kept at a minimum. Polypharmacy must not be permitted to cloud the results; only those agents necessary to protect against shivering or those which may be clearly demonstrated to reduce fibrillation should be used. Moreover, until further knowledge lends safety, the experience should be gained primarily in the experimental laboratory. Here legitimate controls may be established, objective data obtained, and statistical evidence justified.

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REFERENCES

1. Laborit, H.: Réaction organique à l'agression et choc, Paris, Masson et Cie, 1952.
2. Dundee, J. W.; Gray, T. C.; Mesham, P. T., and Scott, W. E. B.: Hypothermia with Autonomic Block in Man, *Brit. M. J.* **2**:1237, 1953.
3. Martin, C. J.: Thermal Adjustment of Man and Animals to External Conditions, *Lancet* **2**:561-567, 1930.
4. Bigelow, W. G.; Callaghan, J. C., and Hopps, J. A.: General Hypothermia for Experimental Intracardiac Surgery: Use of Electrophrenic Respirations, an Artificial Pacemaker for Cardiac Standstill and Radio-Frequency Rewarming in General Hypothermia, *Ann. Surg.* **132**:531-539, 1950.
5. Smith, L. W., and Fay, T.: Temperature Factors in Cancer and Embryonal Cell Growth, *J. A. M. A.* **113**:653-660, 1939.
6. Swan, H.; Zeavin, I.; Holmes, J. H., and Montgomery, V.: Cessation of Circulation in General Hypothermia: I. Physiologic Changes and Their Control, *Ann. Surg.* **138**:3, 360-376, 1953.
7. Prevedel, A. E.; Montgomery, V., and Swan, H.: Effect of Coronary Perfusion of Prostigmine on Ventricular Fibrillation in the Hypothermic Dog, *Proc. Soc. Exper. Biol. & Med.* **85**:596-597, 1954.
8. McQuiston, W. O.: Anesthetic Problems in Cardiac Surgery in Children, *Anesthesiology* **10**:590-600, 1949.
9. Dagliotti, A. M., et Ciocatto, E.: Les bases physiopathologiques de l'hypothermie et les possibilités de l'association hypothermie-circulation extracorporelle, *Schweiz. med. Wchnschr.* **83**:31, 707-710, 1953.
10. Cookson, B. A.; Neptune, W. B., and Bailey, C. P.: Hypothermia as a Means of Performing Intracardiac Surgery under Direct Vision, *Dis. Chest* **22**:245, 1952.
11. Lewis, F. J., and Taufic, M.: Closure of Atrial Septal Defects with Aid of Hypothermia: Experimental Accomplishments and Report of One Successful Case, *Surgery* **33**:52, 1953.